AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Formerly The American Fertility Society

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April 19, 2005

Jesse Goodman MD, MPH
Director
Center for Biologics Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Pending Implementation of Donor Testing Requirements for Reproductive Tissue

Dear Dr. Goodman:

Thank you for agreeing to meet with representatives of the American Society for Reproductive Medicine ("ASRM") and the Society for Assisted Reproductive Technology ("SART") on April 25, 2005 to discuss the upcoming implementation of FDA's Eligibility Determination of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 21 CFR 1271.45, *et seq.* As you know, ASRM/SART and Center for Biologics Evaluation and Research ("CBER") have worked closely together for many years concerning application of the communicable disease provisions of the Public Health Service Act to reproductive tissues. Due to your cooperation and that of your staff, we have resolved many potential conflicts, and we thank you for your continued willingness to work toward a solution to these complex issues.

ASRM/SART remain concerned about the impact of donor testing requirements on assisted reproductive technologies, particularly embryo and oocyte donation.[1] Although many of the donor testing requirements are reasonable and form the backbone of the practice of reproductive medicine, the requirement that physicians collect donor specimens at the time of cell recovery or "up to 7 days before or after

[1] *See* ASRM, Comments Submitted to Docket No. 2004D-1093 (Aug. 23, 2004); ASRM, Comments Submitted to Docket No. 97N-484S (Dec. 29, 1999).

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recovery" is problematic. *Id.* at 29832. Simply put, there is little scientific basis for FDA's May 2004 determination that testing must be performed in such close proximity to recovery of reproductive tissue. In fact, FDA recently re-opened the comment period concerning application of the good tissue practice regulations ("GTP") to reproductive tissue so that it can further examine the risk of disease transmission posed by these tissues. FDA: *Questions and Answers for Roll-Out of GTP Final Rule*, November 23, 2004. The same analysis should also lead to suspension of the impending testing requirements for reproductive tissue donors.

I. Background

On May 25, 2004, FDA published a final rule requiring human cell, tissue, and cellular and tissue-based products (HCT/P) establishments to screen and test donors for communicable diseases. 69 Fed. Reg. at 29786. The rule was promulgated as part of FDA's comprehensive regulatory program for HCT/Ps initiated in March 1997. *Id.*

The final rule sets out extensive and mandatory donor screening procedures. Among the specific requirements, the final rule provides that reproductive medicine physicians "collect the donor specimen at the time of recovery of cells.... [or] up to 7 days before or after recovery." 69 Fed. Reg. at 29832. In promulgating the rule, FDA asserted about tissue donors generally that "testing for communicable disease performed later than 7 days before donation...would not accurately reflect the donor's actual disease exposure at the time of donation." *Id.*

But, in November 2004, the agency expressed a willingness to reevaluate the "communicable disease risks associated with reproductive" tissues and the "appropriate regulation [necessary] to minimize those risks." FDA: *Questions and Answers for Roll-Out of GTP Final Rule*, November 23, 2004. To ensure a full understanding of the risk associated with reproductive tissues, FDA refrained from finalizing proposed rules concerning the applicability of GTP to reproductive human tissue. *See* 69 Fed. Reg. 68612 (November 24, 2004). Nevertheless, donor eligibility requirements for such tissue donors will become effective on May 25, 2005. 69 Fed. Reg. 29786 (May 25, 2004).

Consequently, reproductive medicine practice groups are now in an awkward position. We are prepared to implement additional donor testing in

compliance with the rules, yet FDA has acknowledged that the benefit of this testing has not been quantified. This is troublesome because added testing requirements are likely to dramatically reduce the availability of reproductive tissue for donation, without reducing risks, all at a time when demand for embryos and oocytes is growing.

Moreover, the donor eligibility requirements come dangerously close to overstepping the line between appropriate regulation of manufacturing and state regulation of the practice of medicine. At SART member clinics, state-licensed physicians perform medical services in a private setting involving the most delicate and personal issues. FDA should not impose a governmental presence into this process by imposing unworkable requirements and schedules for tests of unknown value.

For these reasons, we ask that you suspend implementation of proposed section 21 CFR 1271.80(b) (timing of specimen collection) as it applies to human embryos and oocytes and receive additional comments on the proposed timeframe for appropriate donor testing.

II. Oocyte Donation for use in Assisted Reproduction

There are two general categories of infertility treatment: insemination and assisted reproductive technology (ART). *See* ASRM, Comments to Docket No. 97N-484S (Dec. 29, 1999). In vitro fertilization (IVF) is a method of assisted reproduction in which sperm and oocyte are combined in a laboratory dish, where fertilization occurs. The resulting embryo is then transferred to the uterus to develop naturally. The ooyctes for IVF may come either from the woman seeking IVF treatment[2] or from a donor. Both scenarios will be adversely affected by the 7 day donor testing requirement that becomes effective on May 25, 2005, as explained below.

A. IVF Treatment

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[2] When a woman is part of a sexually intimate couple seeking treatment, FDA has exempted the couple and the resulting reproductive tissue from the scope of the tissue regulatory scheme. 69 Fed. Reg. 686612, 28829 (proposed May 25, 2004) (to be codified at 21 C.F.R. pt. 1271.90(a)(2)).

Women who pursue IVF treatment in order to later receive a resulting embryo for implantation and pregnancy first undergo an initial evaluation, which may include physical and psychological screening. HANDBOOK OF IN VITRO FERTILIZATION 485-86 (Alan O. Trounson & David K. Gardner eds., 2000). Because the couple is generally sexually intimate and using their own gametes, donor screening and testing is not required.

The woman then begins the IVF process and is placed on a regime of fertility drugs that will stimulate increased ovulation. *See, e.g.,* New York University Program for In Vitro Fertilization, Reproductive Surgery & Infertility, *available at* http://nyuivf.med.nyu.edu/services/donor.html; Johns Hopkins Medical Institution, Department of Gynecology and Obstetrics, Reproductive Endocrinology & Infertility, *available at* http://womenshealth.jhmi.edu/rei/. Once oocytes are mature, they are retrieved from the woman and assessed by an embryologist to determine the appropriate timing of insemination. HANDBOOK OF IN VITRO FERTILIZATION, *supra* at 76. Oocytes are generally incubated for a minimum of 3 to 6 hours and fertilized with sperm. *Id.* at 129. Approximately three days after oocyte retrieval, resultant embryos (usually two) are transferred to the uterus for implantation. *See* New York University Program for In Vitro Fertilization, *supra.*

Remaining embryos may be frozen for future use by the couple should implantation fail, or should they wish to pursue additional future conceptions. *Id.* Any embryos not used by the couple may be donated for use by another person or couple. It is these donations that are imperiled by the impending regulation. Under the rule, couples who wish to donate unused embryos at some point in the future must elect screening for communicable diseases within 7 days of oocyte retrieval.

However, couples pursuing IVF generally are focused on their own efforts to achieve pregnancy—not on the possibility of donating excess embryos at some point in the future. Because donor screening and testing is not required for sexually intimate couples, very few will opt to incur the considerable expense of such testing on speculation that they may one day want to donate an embryo. Of course, if they forgo such testing, the 7 day rule prevents a donation should the couple later decide to donate and would necessitate that the excess embryos be discarded—an ethically problematic decision for many couples. For those couples who elect screening but have no excess embryos, the screening is simply a waste of resources. Indeed, many couples will have no embryos to donate at all by the end of their IVF treatment.

B. Oocyte Donors

When sexually intimate couples cannot conceive with the woman's oocyte, many turn to oocyte donation. The oocyte donation process is long, complex, and emotionally demanding for all involved. Throughout, the reproductive medical professionals seek to assure that risks are minimized, the emotional strain is managed, and the process remains as simple as possible. To assist our members and their patients in these treatments, ASRM/SART have published numerous reports on the clinical aspects of gamete donation, including how to provide appropriate screening, as well as providing guidance on the ethical questions raised.

Before initiation of the donation process, oocyte donors are screened extensively. HANDBOOK OF IN VITRO FERTILIZATION, *supra* at 487-88. A nurse or clinician interviews the donor about her medical, social, and physical history. *Id.* All donors should have at least one extended counseling session to discuss the donation decision. *Id; see also*, Johns Hopkins Medical Institution, *supra.*

Once a woman has been accepted as a potential donor, couples seeking donations may review information about her such as physical characteristics (e.g., skin color, eye color, hair color and body build), medical (e.g., blood group & Rh factor) and psychological profile (e.g., ethnic background). *See, e.g.*, The Center for Reproductive Health, "Egg Donation," *available at* http://www.reproductivehealthctr.com/index.htm; Duke University Reproductive Endocrinology and Infertility, "Information for Oocyte Recipients," *available at* http://www2.mc.duke.edu/depts/obgyn/ivf. If a match is found, the potential donor undergoes extensive clinical examination and testing, including blood tests, a Pap Smear, cervical cultures, and possibly genetic and drug testing. New York University Program for In Vitro Fertilization, *supra.*

After this testing, if the donor is suitable, she begins taking medication for 3-4 weeks which stops her normal menstrual cycle. *Id.* Once her cycle is halted, she receives follicle stimulating hormones to stimulate her ovaries to produce multiple oocytes. *Id.* When blood tests and ultrasound indicate the oocytes are mature, they are harvested, often through the use of a transvaginal needle, and are fertilized with sperm, either from the male of the couple being treated or from a sperm donor. HANDBOOK OF IN VITRO FERTILIZATION, *supra at* 68, 73, 127-140.

At this point in the donation process, the 7 day rule would impose a second round of testing duplicative of that performed at the time of donor matching. ASRM/SART does not dispute the fundamental premise that donor testing for communicable disease is required to minimize those risks. However, the question remains whether the first round of tests are adequate to screen for those diseases.

Oocyte donation programs are facing "an increasing challenge of obtaining an adequate supply of donated eggs to meet their growing demand." HANDBOOK OF IN VITRO FERTILIZATION, *supra at* 484. Studies cite the invasiveness of the screening and collecting procedures as the major deterrents to donation. *Id.* With the number of women seeking IVF increasing each year, it is essential that donation not be hindered unnecessarily by more burdensome testing requirements. *See* 2002 CDC DIVISION OF REPRODUCTIVE HEALTH, ASSISTED REPRODUCTIVE TECHNOLOGY (ART) SUCCESS RATES (Dec. 2004).

ASRM/SART certainly find it reasonable for donors to undergo standardized infectious disease risk assessment. Indeed, all SART member clinics are required, as a condition of membership, to adhere to these and all other guidelines. As such, to the extent possible, additional donor testing should be minimized. Nevertheless, should additional testing be required to adequately protect the public health, it is not at all clear that the 7 day window is appropriate. It is extremely difficult to precisely gauge when oocyte retrieval will occur. Retrieval timing depends on oocyte development which is highly variable across donors. Thus, under the 7 day rule, testing samples could easily be inadvertently obtained more than 7 days before retrieval – requiring yet another round of patient testing. Of course, these tests are taxing on the donor and add a substantial cost for the couple seeking treatment.

III. Request for Stay of Regulation

Because embryo and oocyte donation are likely to decrease dramatically under the regulation and because FDA has already indicated a willingness to re-evaluate the risks posed by these tissues, ASRM/SART requests that FDA suspend application of the 7 day testing requirement as it applies to embryo and oocyte donors and expand the scope of the comments currently being accepted concerning reproductive tissues.

A. Precedent for Stay

FDA may suspend application of a published regulation before the effective date if the Commissioner determines that it is in the public interest to do so. 5 USC 553(e); 21 CFR 10.35(a) and (d)(1). Indeed, FDA has suspended published final rules where it determined that the public interest would benefit from further consideration of outstanding questions contained in or raised by the rule. *See, e.g.*, 65 Fed. Reg. 25639 (May 3, 2000)(delaying effective date and reopening the record to allow additional time for FDA to consider, *inter alia*, the possibility that the rule may inhibit the ability of blood centers to provide products to the public). And, the agency has suspended rules that potentially threaten the viability of the industry or products they seek to regulate. *See id*; 62 Fed. Reg. 15390 (Apr. 1, 1997)(staying the nutrient content claim regulations pertaining to the use of the term "healthy," in response to concerns that consumers would not accept alternative low-sodium food).

The case for a stay is especially compelling when the agency anticipates amending or developing policy related to the regulation as is the case here. In 2001, FDA stayed the final monograph for over-the-counter sunscreen drug products to allow for development of a more comprehensive monograph that addressed testing requirements for UVA radiation protection. 66 Fed. Reg. 67485 (Dec. 31, 2001). The agency observed that it would be impossible (and impracticable) to require manufactures to label and test products in accord with a amended final monograph when no such monograph had been published. *Id.* Because FDA continues to assess whether and how to apply GTP to reproductive tissues, it should take the opportunity to further assess the usefulness of the 7 day donor testing requirement as it applies to those tissues.

Alternatively, a stay should be granted to examine the impact of the donor eligibility rule as it relates to the independent practice of medicine. It is well established that FDA does not have jurisdiction to regulate the administration of a drug or use of a device by a physician. *See, e.g., U.S. v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981); *C.f. Buckman Company v. Plaintiff's Legal Committee*, 531 U.S. 341, 350-351 (2001). The FDA itself has said, "Congress did not intend the [FDA] to interfere with medical practice . . . [or] to regulate the practice of medicine as between the physician and the patient." 37 Fed. Reg. 16,503 (1972).

Admittedly, the line between FDA's jurisdiction over communicable diseases under the PHSA and the practice of medicine is not sharply defined. Historically, however, "[t]ransplantation was regarded as part of the practice of medicine or surgery, and no effort was made to regulate the procedure or the

human organs and tissues being transplanted... FDA [merely] encouraged the development of voluntary guidelines by those who retrieved, processed, and stored human tissue intended for transplantation." Stuart L. Nightingale, FDA Regulatory Philosophy, 46 Food Drug Cosm. L.J. 4 (1991). Even as Congress and the agency have acted to regulate various aspects of tissue donation, they have made efforts to recognize the strong self-regulation of the medical profession and preserve physicians' autonomy over the practice of medicine. *See, e.g.,* 42 USC 263a-2(i)(1) (2000). ("In developing the [embryo laboratory] certification program, the Secretary [of HHS] may not establish any regulation, standard, or requirement which has the effect of exercising supervision or control over the practice of medicine in assisted reproductive technology programs."). By contrast, the donor eligibility rule threatens to remove from the physician a long-recognized ability to make treatment choices based on patients' personal needs by defining with precision the content and timing of donor testing.

B. Public Interest Favors Stay of 7-Day Rule

Common sense dictates that FDA take the opportunity to simultaneously assess the risks associated with reproductive tissue and the testing requirements for donors of such tissue. Quite simply, FDA should refrain from imposing an impractical and potentially damaging regulatory change without an clear understanding of the risk of disease transmission.

Alternatively, ASRM/SART believe that regulatory alternatives exist that would adequately protect public health while easing the burdens on donors. For couples who are not required to be tested under the regulation, screening can be performed and embryos released if and when the couple determines they wish to donate embryos.

Outside of sexually intimate relationships, screening is already an integral part of the initial review of potential oocyte donors. We ask FDA to consider whether this testing already serves to protect embryo recipients and to abandon the 7 day testing requirement as applied to these donors.

If the agency considers and rejects this alternative, we urge you to extend the 7 day window to 30 days for oocyte donors. This would allow donor eligibility testing to be conducted a second time before the donor undergoes follicle stimulating hormone treatment for the purpose of oocyte retrieval. This would avoid unnecessary exposure to the medications, invasive procedures and costs

should any given screening test be positive. Although it is theoretically possible to do this testing in a shorter window before oocyte retrieval, it is difficult to accurately estimate the time of retrieval. To be most practical, we believe a 30 day window would insure that all donors are adequately tested at the time they begin undergoing intensive medical treatment designed to facilitate their oocyte donation. With regards to embryo donation, we urge you to extend the window to within 30 days prior to the donation of the embryos, and not the procurement of the reproductive tissue.

IV. Conclusion

We thank you again for the opportunity to discuss these issues with you and appreciate the time and attention you will devote to assisting us their resolution.

Sincerely,

Robert W. Rebar, MD

Robert W. Rebar, MD
Executive Director
ASRM

Eric Surrey, MD
President
SART

cc: Lester Crawford DVM, Ph D, Acting Commissioner, Food and Drug Administration

Rear Admiral Cristina V. Beato, M.D., FAAFP
Acting Assistant Secretary for Health
U.S. Department of Health and Human Services (HHS)